Registration of Users and Distribution of Living Anopheles Vector Mosquitoes by the MR4

Last Updated: Feb 2006

INTRODUCTION

As part of the MR4 activities, living Anopheles mosquitoes will be distributed worldwide. These materials are intended as seed stock or as references that will require cultivation at the destination. Because eggs are most easily shipped, we will routinely ship eggs - either dried or on damp filter paper - to requesters from the MR4 vector repository at the Centers for Disease Control in Atlanta, Georgia, USA.

Risk of receiving and culturing Anopheles at the destination reflects numerous factors including local malaria transmission history, the facilities that will house the insects, the duration of their cultivation, and even micro-climate. Since the risk of cultivating mosquitoes at all destinations is not readily ascertained, case-by-case hazard assessments will be performed. We address this process and related issues under 'Registration and Distribution' below.

Finally, we provide general considerations for evaluating hazards, and elaborate on the principles that shaped these recommendations under 'Principles of Risk Assessment.'

REGISTRATION

Registration for users anticipating shipments of living vector material will be according to the standard procedure.

REVIEW COMMITTEE

Requests for living material will be considered by the review committee at the time they are received at the CDC. As of Feb, 2006, the review committee consists of:

Chris Curtis

Mark Benedict

Ken Vernick

Greg Lanzaro

Bart Knols

Barbara Sina

Adriana Costero

DISTRIBUTION

The Requesters Responsibility for Assuring Minimal Risk

The primary burden of assessing hazard will be in the hands of the authorities governing receipt and maintenance of the live vector materials. Documentation may be requested indicating that an import permit for the material is not required by the requester's country, or an import permit must be provided to the MR4.

Before shipments are made, both domestic and international, the MR4 may request documentation from the requester, their receiving institution, its biosafety committee, or the local or regional authority that confirms that appropriate containment and maintenance facilities are available for the materials and described use in the registration material. The MR4 review committee will determine, depending on the potential hazards, whether specific additional information will be required. The information requested may include specifics regarding:

1. Appropriate incubators or rooms in which the temperature and humidity can be controlled in a range compatible with anopheline culture
2. The number and type of physical barriers that prevent accidental escape of vectors
3. The method of trapping adults and preventing escape of live immature stages through the drain system
4. The method that will be used for killing immature and adult stages before disposal
5. In the event of accidental release, describe local climate characteristics that will (or will not) prevent establishment of the specific vectors requested.
6. Whether there is, or has been, local transmission of malaria and the identity of vectors that have been implicated
7. Whether the vector species requested already occur at the destination or in contiguous regions from which immigration could reasonably be expected to occur

Once the requested materials are received by the MR4, the advisory sub-committee that reviews requests for live material will consider the request using materials distributed by e-mail or FAX.

MR4 Review

After review of a request for live vectors is complete, the MR4 may either approve the request, approve the request for some of the species or stocks requested, or may deny shipment of live vectors if it reviews the above description and believes significant risk exists. The requester will be notified and remediation, if possible, can be made in response to the risk factors identified by the MR4. If acceptable risk reduction cannot be made, the MR4 will not ship live material. Approvals will be valid for the entire three years of user registration unless significant alterations of conditions at the destination occur that would increase risk.

Embargoed Countries

International shipments to U.S. embargoed countries (Albania, Angola, Bosnia & Herzegovina, Cambodia, Cuba, Iran, Iraq, Libya, North Korea, Rwanda, Syria, and Serbia and Montenegro (Countries of the former Fed. Republic of Yugoslavia) will not be made without approval from the Dept. of Commerce, Bureau of Export Administration (DOC/BXA).

PRINCIPLES OF HAZARD ASSESSMENT

We anticipate that requests for vector stocks will come from locations in which the vector may or may not already occur. The former case can be expected when the request is for a stock that is a reference standard and/or is more easily cultivated than the available local mosquitoes. The latter situation is expected generally to be laboratory experimentation that may or may not require long-term cultivation. In either case, accidental escape should be prevented, but the risk attending these is not equal.

The most relevant risk considerations, which must be considered as intersecting variables are: (1) whether the vector is, or could become established in the destination and (2) whether the area is, or is potentially, malarious, or has a history of malaria transmission. The permutations and our estimation of the attendant risks are represented in the following table:

Risk Assessment Matrix

	Destination Classification		
Vector Classification	Malarious	Potentially Malarious	Non-Malarious
Incompatible	Moderate	Low	Low
Indigenous	Low	Low	Low
Compatible	High	High	Moderate

Definitions

Destination Classifications

Malarious: clinical cases of malaria occur each year due to locally contracted infections (i.e. endemic and seasonally epidemic regions)

Potentially malarious: clinical cases of malaria have been commonly reported in the past due to locally contracted infections, however cases are not commonly reported at present (e.g. malaria once occurred, but has been eradicated regionally, or unusual climatic conditions were necessary for a rare epidemic)

Non-malarious: local transmission of malaria has never been reported or the frequency is negligible (e.g. airport malaria)

Vector Classification

Incompatible: The vector species does not occur at any season of the year in the proximity of the destination although the species may occur in contiguous regions, and climate is believed to prohibit migration and establishment at the proposed research location. Examples would be tropical species limited by the climate of an altitude or latitude, but no other barrier appears to limit immigration and establishment. The destination climate and biotype are not similar to the regions in which the vector is known to occur.

Compatible: While the vector does not occur in the vicinity, importation and accidental release could reasonably be expected to result in establishment of the species due to the similar climate/biotype of the destination to that of the region in which it is commonly collected

Indigenous: Collections of the species can be made at some season each year either in the proximity of the destination or in contiguous areas from which migration might reasonably be expected

These risk estimations in the above table are species specific. Documentation from the requester may be required by the MR4 to describe and categorize the above risk characteristics.

Explanation of High Risk

Under no circumstances will live mosquitoes be shipped to high-risk areas. It is difficult to envision a case in which the necessity of performing the research in such an area would justify risking accidental release and establishment. Therefore, the risk of accidental introduction of a novel vector into malarious areas warrants that the research be performed elsewhere.

Explanation of Moderate Risk

Mosquitoes will be shipped to moderate risk locations only if the criteria described in the vector repository proposal are met. We expect the advisory committee to elaborate on these criteria (section 9 of Proposal, 'Distribution,' reiterated below):

"… (1) credible scientific interest in the materials, (2) ability to assure national and/or regional permission to import, (3) adequate environmental controls to sustain the materials provided, (4) an approved physical containment laboratory must house the mosquitoes, (5) acknowledgment of the source in publications and, (6) agreement to not distribute the living materials to any other laboratory."

We particularly emphasize that the physical containment in '(4)' should be of a nature that escape is physically prevented through ventilation systems, doorways, access passages, and sewage systems. Furthermore, all material to be discarded will be killed before disposal. No living insect of any stage should be allowed to escape from any insectary portal.

Explanation of Low Risk

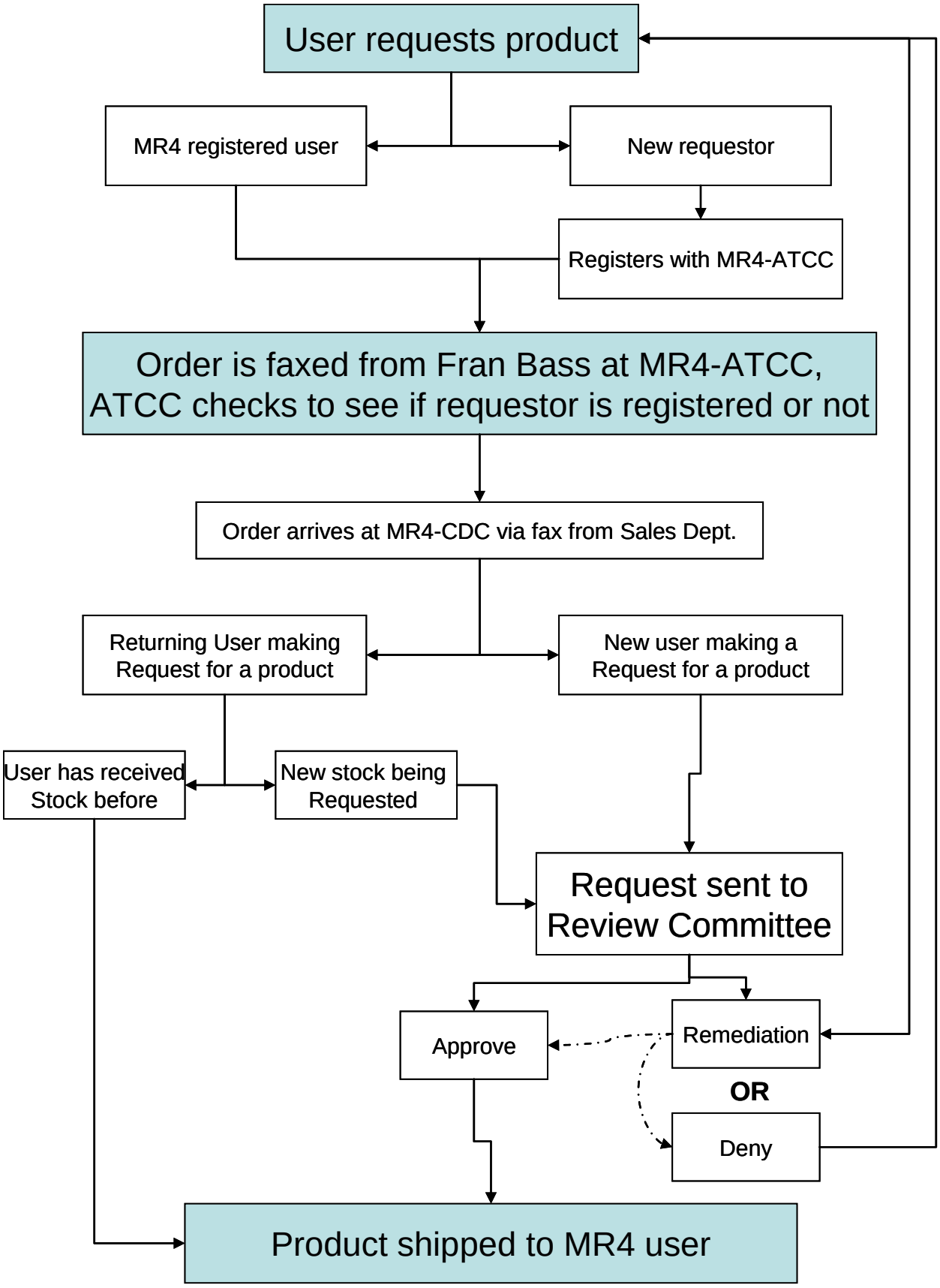
We consider all cases in which the vector is indigenous low risk. Significant risk would exist only if the colony requested had acquired novel characteristics in the colonization and maintenance process that were not pre-existing in wild populations. The strains that have been proposed for distribution have been established from wild mosquitoes without deliberate selection beyond ability to be colonized and, for genetic stocks, induced mutations. Since the pheno-/genotypes

requisite for colonization were already present in the wild populations (e.g. stenogamy, container-oviposition behavior, laboratory host blood-feeding behavior), colonization consists primarily of increases in the frequency of these pheno-/genotypes during colony amplification. It is implausible that neomorphs would arise during colonization and maintenance that would have both a significant positive effect on the vector competence and reproductive fitness. Furthermore, if novel combinations of alleles did increase in frequency in the laboratory, recombination in natural populations would quickly eliminate these combinations.

Therefore, in the event of accidental release, mosquitoes with such genotypes present little risk of either becoming predominant in wild populations or increasing the vector competence of the population. Similarly mutant sub-lines pose little risk since the mutations that were purified were either pre-existing in the colonized population or result from gene damage due to mutagenesis and are predominantly less fit than wild type.

Live mosquitoes will be shipped to destinations of low risk, though condition ‘4’ above (physical containment) will be reduced to a level necessary to reasonably prevent release, but will not be as stringent as that required for shipments to areas of moderate risk.

In all cases, the MR4 will require adequate documentation to substantiate the above conditions. Regardless, notification of intention to ship live materials will be made to ATCC by the CDC prior to shipment, and copies of records of all request communications will be maintained at the CDC.


User requests product
MR4 registered user
New requestor
Registers with MR4-ATCC
Order is faxed from Fran Bass at MR4-ATCC, ATCC checks to see if requestor is registered or not
Order arrives at MR4-CDC via fax from Sales Dept.
Returning User making Request for a product
New user making a Request for a product
User has received Stock before
New stock being Requested
Request sent to Review Committee
Approve
Remediation
OR
Deny
Product shipped to MR4 user